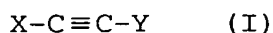


## Preparation of organic alkyne compounds

The present invention relates to a process for preparing organic  
5 alkyne compounds of the formula I



by reacting organic halogen compounds of the formula Ia

10



with organic terminal alkyne compounds of the formula Ib

15



where X and Y are identical or different organic radicals and Hal  
is chlorine or bromine, in inert solvents under the action of  
microwave energy, in the presence of at least one metal compound  
20 and at least one base.

Under the customary conditions of the Sonogashira reaction, aryl  
or alkenyl halides are reacted with terminal alkyne compounds  
under palladium and copper salt catalysis at elevated temperature  
25 to give correspondingly substituted alkyne compounds.

A distinct reduction in the reaction time can be achieved by  
carrying out the reaction under the action of microwave  
radiation.

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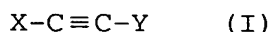
For instance, J.-X. Wang et al. (J. Chem. Research (S), 2000, p.  
536-537) describe reactions of different terminal alkynes with  
organic iodine compounds in the presence of copper(I)  
iodide/triphenylphosphine and potassium carbonate in  
35 dimethylformamide (DMF). The comparison of the reactions show in  
table 2 of this publication, on the one hand under reflux of DMF,  
and on the other hand under the action of a microwave radiation  
source having an output of 375 W shows impressively that when  
comparable yields are obtained, the reactions in the latter case  
40 proceed more quickly than in the former case by factors of from  
48 to 144.

Investigations of solvent-free reactions of aryl, heteroaryl and  
vinyl iodides with terminal alkynes in the presence of  
45 palladium/copper(I) iodide/triphenylphosphine and potassium  
fluoride supported on aluminum oxide under the action of  
microwave radiation have been carried out by G.W. Kabalka et al.

(Tetrahedron Lett. 41, 2000, p. 5151-5154). The authors mention (p. 5152) that aryl chlorides and bromides did not react and that the starting materials were recovered unchanged.

- 5 We have now been found that, surprisingly, organic chlorine and bromine compounds can be reacted with terminal organic alkyne compounds to give alkyne derivatives in good to very good yields.

Accordingly, a process has been found for preparing organic  
10 alkyne compounds of the formula I



by reacting organic halogen compounds of the formula Ia  
15



with organic terminal alkyne compounds of the formula Ib



where X and Y are identical or different organic radicals

in inert solvents under the action of microwave energy,  
25

in the presence of at least one metal compound and at least one base, wherein Hal is chlorine or bromine.

In this context, inert solvents are liquids or liquid mixtures  
30 which under the reaction conditions react neither with the reactants nor with the products.

In particular, such inert solvents are polar, aprotic liquids, since the use of protic liquids may lead to undesired secondary  
35 reactions which are triggered off by protonation.

To simplify the discussion, the terms "solvent" and "dissolve" will hereinbelow be used, even when in individual cases, for example, the base or bases or metal compound or metal compounds  
40 used are not completely dissolved, but are instead in suspension (or emulsion).

Preference is given to using those metal compounds which comprise a metal selected from the group consisting of magnesium, calcium,  
45 strontium, barium, titanium, zirconium, hafnium, iron, ruthenium, osmium, cobalt, rhodium, iridium, nickel, palladium, platinum,

## 3

copper, silver, gold, zinc, cadmium and mercury. Particular preference is given to using copper compounds.

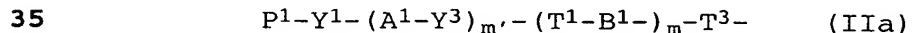
Emphasis is given to the metal halide compounds, in particular the chlorides and bromides, but also the iodides, of the metals mentioned. When these halides form adducts with triarylphosphines, for example triphenylphosphine, they are advantageously used in the form of these adducts.

10 Metal compounds further include the metals themselves, in particular the abovementioned metals in elemental form. Furthermore, combinations of more than one metal compound, more than one metal, and also combinations of metals and metal compounds may be used. The metal species which is catalytically  
15 active in the reaction does not necessarily have to be identical to the metal compounds added, but can instead only be formed in situ by reaction with the reactants and/or the base or bases.

The organic radicals X and Y are saturated or unsaturated  
20 hydrocarbon radicals, and also hydrocarbon radicals which contain both saturated and unsaturated moieties. The hydrocarbon radicals may further contain customary heteroatoms, such as nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, bromine or iodine. The organic radicals X and Y customarily have molar  
25 masses of up to about 600 g/mol. However, in individual cases, the molar masses of the X and Y radicals may also be higher.

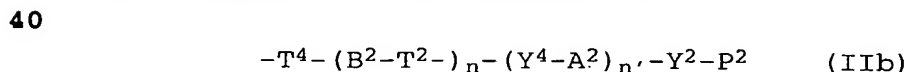
Preferred organic radicals X and Y contain saturated or unsaturated carbo- or heterocyclic radicals where both -Hal, i.e.  
30 chlorine or bromine, and  $H-C\equiv C-$  are bonded directly to the saturated or unsaturated carbo- or heterocyclic radicals.

In particular, X is a radical of the formula IIa



and

Y is a radical of the formula IIb



where

45

4

P<sup>1</sup> and P<sup>2</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>2</sub>-alkyl, a polymerizable group, a group suitable for polymerization or a radical which carries a polymerizable group or a group suitable for polymerization,

5

or

P<sup>1</sup> and/or P<sup>2</sup> each corresponds to a radical P<sup>1'</sup> and/or P<sup>2'</sup> which denotes a precursor group which is stable under the reaction conditions which can be reacted to give the corresponding polymerizable group or group suitable for polymerization P<sup>1</sup> and/or P<sup>2</sup> or the radicals P<sup>1</sup> and/or P<sup>2</sup> which carry a polymerizable group or a group suitable for polymerization,

15 Y<sup>1</sup>, Y<sup>2</sup>, Y<sup>3</sup> and Y<sup>4</sup> are each independently a single chemical bond, -O-, -S-, -CO-, -CO-O-, -O-CO-, -CO-N(R)-, -(R)N-CO-, -O-CO-O-, -O-CO-N(R)-, -(R)N-CO-O- or -(R)N-CO-N(R)-,

20 B<sup>1</sup> and B<sup>2</sup> are each independently a single chemical bond, -C≡C-, -O-, -S-, -CO-, -CO-O-, -O-CO-, -CO-N(R)-, -(R)N-CO-, -O-CO-O-, -O-CO-N(R)-, -(R)N-CO-O- or -(R)N-CO-N(R)-,

25 each R is, independently and irrespective of the meaning in each of Y<sup>1</sup> to Y<sup>4</sup>, B<sup>1</sup> and B<sup>2</sup>, hydrogen or C<sub>1</sub>-C<sub>4</sub>-alkyl,

A<sup>1</sup> and A<sup>2</sup> are each independently spacers having from 1 to 30 carbon atoms,

30

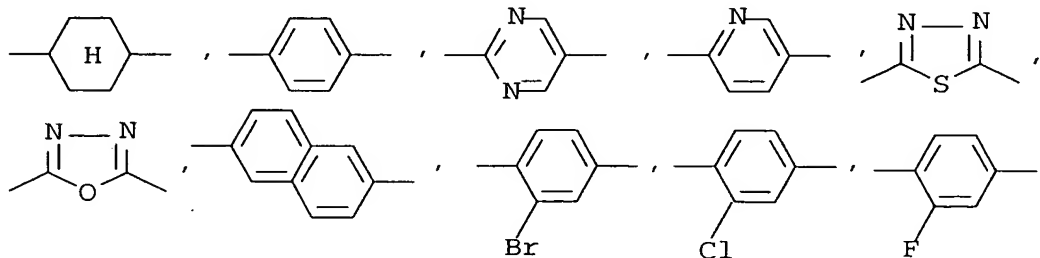
T<sup>1</sup>, T<sup>2</sup>, T<sup>3</sup> and T<sup>4</sup> are each independently bivalent, saturated or unsaturated, carbo- or heterocyclic radicals and

m', m, n' and n are each independently 0 or 1.

35

The T<sup>1</sup> to T<sup>4</sup> radicals in the formulae IIa and IIb are in particular those selected from the group consisting of

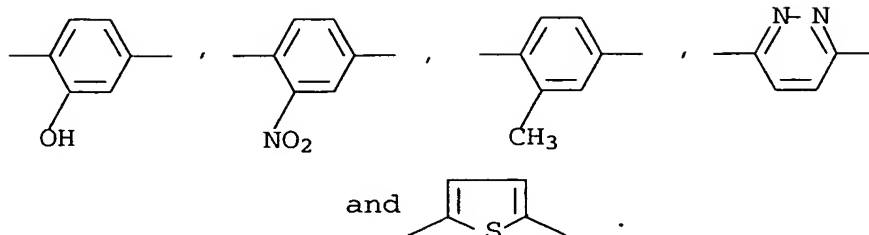
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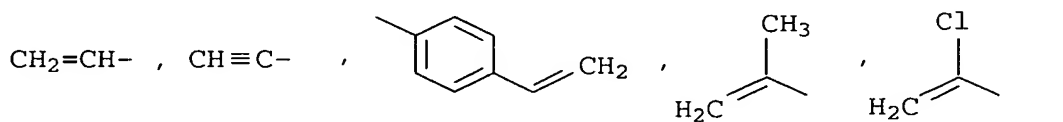


Useful  $C_1$ - $C_{12}$ -alkyl radicals for  $P^1$  and  $P^2$  in formula I include  
 10 branched and unbranched  $C_1$ - $C_{12}$ -alkyl chains, for example methyl,  
 ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl,  
 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 1-methylbutyl,  
 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl,  
 n-hexyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl,  
 15 2-methylpentyl, 3-methylpentyl, 4-methylpentyl,  
 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl,  
 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl,  
 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl,  
 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl,  
 20 1-ethyl-2-methylpropyl, n-heptyl, n-octyl, 2-ethylhexyl, n-nonyl,  
 n-decyl, n-undecyl and n-dodecyl.

Preferred  $P^1$  and  $P^2$  alkyl radicals are the branched and unbranched  
 $C_1$ - $C_6$ -alkyl chains, such as methyl, ethyl, n-propyl,  
 25 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl,  
 1,1-dimethylethyl, n-pentyl, 1-methylbutyl, 2-methylbutyl,  
 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl and n-hexyl.

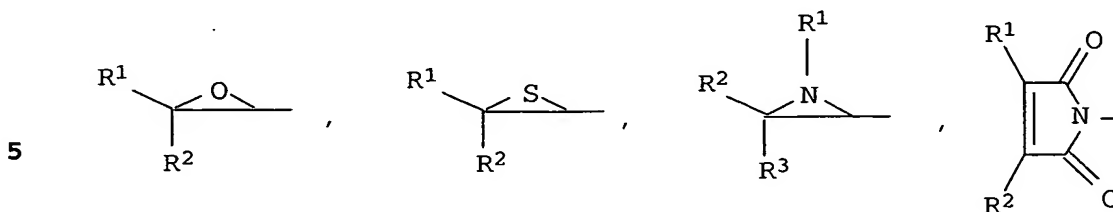
Useful polymerizable groups or groups which are suitable for  
 30 polymerization or radicals which carry a polymerizable group or a  
 group suitable for polymerization (such groups or radicals are  
 referred to hereinbelow simply as "reactive radicals") for  $P^1$  and  
 $P^2$  are in particular:

35



40

45



-N=C=O, -N=C=S, -O-C≡N, -COOH, -OH or -NH<sub>2</sub>,

- 10 where the R<sup>1</sup> to R<sup>3</sup> radicals can be identical or different and are each hydrogen or C<sub>1</sub>-C<sub>4</sub>-alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl.

Useful polymerizable groups for P<sup>1</sup> and P<sup>2</sup> are in particular the  
15 acrylate, methacrylate and vinyl radicals.

Useful C<sub>1</sub>-C<sub>4</sub>-alkyl radicals in the -CO-N(R)-, -(R)N-CO-,  
-O-CO-N(R)-, -(R)N-CO-O- and -(R)N-CO-N(R)- groups listed under  
the bridging units Y<sup>1</sup> to Y<sup>4</sup>, B<sup>1</sup> and B<sup>2</sup> include methyl, ethyl,  
20 n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.  
When one or two R radicals are present in the Y<sup>1</sup> to Y<sup>4</sup>, B<sup>1</sup> and B<sup>2</sup>  
units, any R radicals present in the remaining units may be  
identical or different. The same applies to the case where there  
are two R radicals in one unit.

25

Useful spacers A<sup>1</sup> and A<sup>2</sup> include all groups known to those skilled  
in the art for this purpose. The spacers generally have from one  
to 30, preferably from one to 12, more preferably from one to  
six, carbon atoms and consist of predominantly linear aliphatic  
30 groups. They may be interrupted in the chain by, for example,  
nonneighboring oxygen or sulfur atoms or imino or alkylimino  
groups, for example methylimino groups. Useful substituents for  
the spacer chain include fluorine, chlorine, bromine, cyano,  
methyl and ethyl.

35

Examples of representative spacers include:

-(CH<sub>2</sub>)<sub>u</sub>-, -(CH<sub>2</sub>CH<sub>2</sub>O)<sub>v</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>SCH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>NHCH<sub>2</sub>CH<sub>2</sub>-,

40

-CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)-CH<sub>2</sub>CH<sub>2</sub>-, -(CH<sub>2</sub>CH(CH<sub>3</sub>)CHO)<sub>w</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)-, -(CH<sub>2</sub>)<sub>6</sub>CH(CH<sub>3</sub>)- or -CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)Cl-,

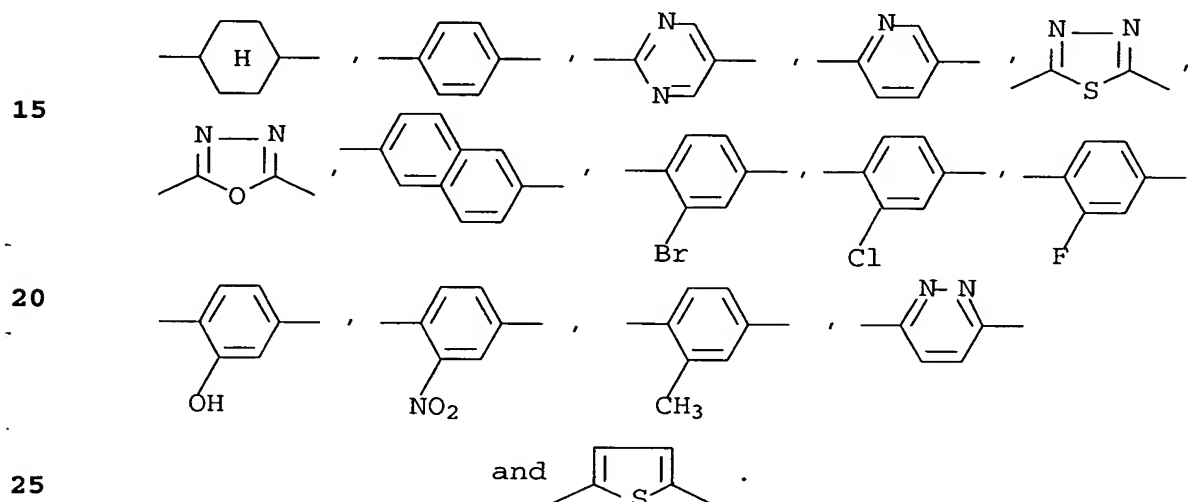
where u, v and w are integers and u is from 1 to 30, preferably  
45 from 1 to 12, v is from 1 to 14, preferably from 1 to 5, and w is  
from 1 to 9, preferably from 1 to 3.

7

Preferred spacers are ethylene, propylene, n-butylene, n-pentylene and n-hexylene.

The T<sup>1</sup> to T<sup>4</sup> radicals are ring systems which may be substituted by  
 5 fluorine, chlorine, bromine, cyano, hydroxyl, formyl, nitro, C<sub>1</sub>-C<sub>20</sub>-alkyl, C<sub>1</sub>-C<sub>20</sub>-alkoxy, C<sub>1</sub>-C<sub>20</sub>-alkoxycarbonyl, C<sub>1</sub>-C<sub>20</sub>-monoalkylaminocarbonyl, C<sub>1</sub>-C<sub>20</sub>-alkylcarbonyl, C<sub>1</sub>-C<sub>20</sub>-alkylcarbonyloxy or C<sub>1</sub>-C<sub>20</sub>-alkylcarbonylamino.

10 Preferred T<sup>1</sup> to T<sup>4</sup> radicals are:



When the reactive P<sup>1</sup> and/or P<sup>2</sup> radicals are unstable under the reaction conditions, the reactants

30 P<sup>1</sup>'-Y<sup>1</sup>-(A<sup>1</sup>-Y<sup>3</sup>)<sub>m</sub>-(T<sup>1</sup>-B<sup>1</sup>)<sub>m</sub>-T<sup>3</sup>-Hal and/or

H-C≡C-T<sup>4</sup>-(B<sup>2</sup>-T<sup>2</sup>)<sub>n</sub>-(Y<sup>4</sup>-A<sup>2</sup>)<sub>n</sub>-Y<sup>2</sup>-P<sup>2</sup>'

may be used as starting materials where the P<sup>1</sup>' and/or P<sup>2</sup>'  
 35 radicals are precursor groups which are stable under the reaction conditions and are converted to or substituted by the corresponding reactive P<sup>1</sup> and/or P<sup>2</sup> radicals in a subsequent step.

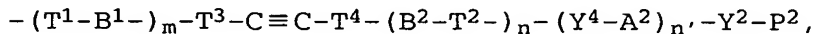
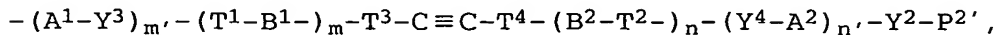
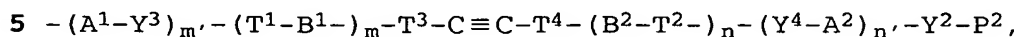
Compounds which, for example, have the construction

40 P<sup>1</sup>'-Y<sup>1</sup>-(A<sup>1</sup>-Y<sup>3</sup>)<sub>m</sub>-(T<sup>1</sup>-B<sup>1</sup>)<sub>m</sub>-T<sup>3</sup>-C≡C-T<sup>4</sup>-(B<sup>2</sup>-T<sup>2</sup>)<sub>n</sub>-(Y<sup>4</sup>-A<sup>2</sup>)<sub>n</sub>-Y<sup>2</sup>-P<sup>2</sup>'

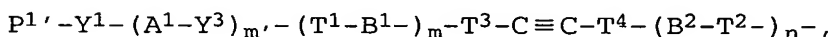
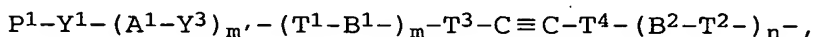
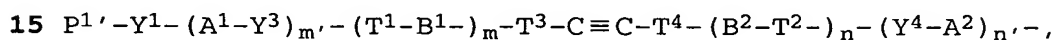
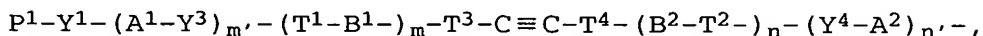
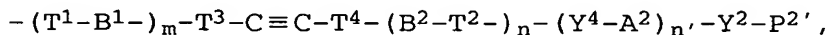
may be regarded as direct products of the preparative process according to the invention.

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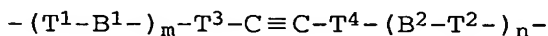
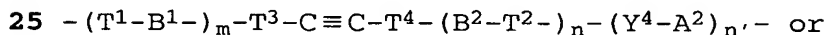
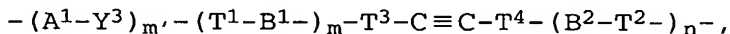
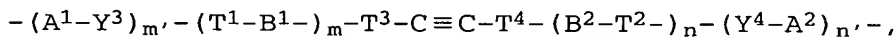
Owing to retrosynthetic considerations, it may also be sensible to prepare the alkyne compounds by the process according to the invention which correspond to the fragments



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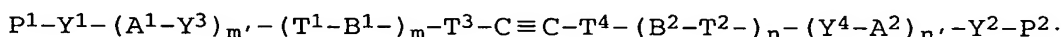


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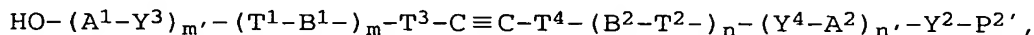
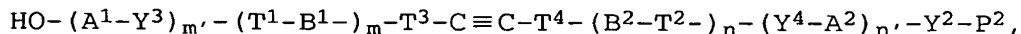
and then convert these in one or more subsequent steps using the appropriate complementary compounds to the target compounds

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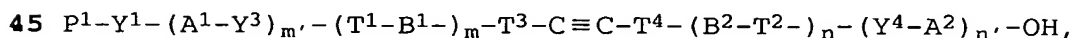
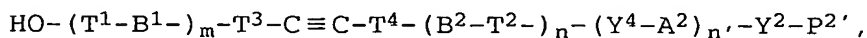
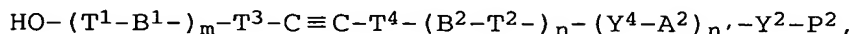


Examples of compounds to which the above-listed fragments correspond include

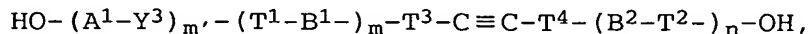
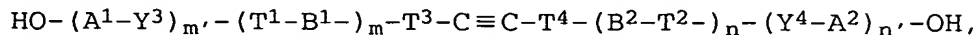
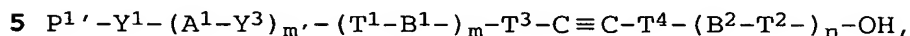
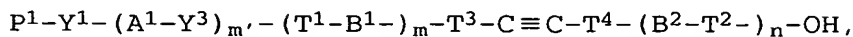
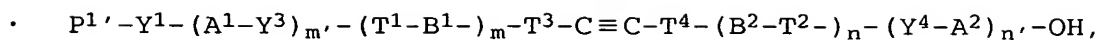
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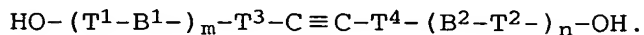
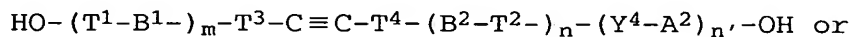
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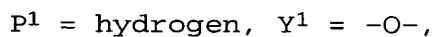




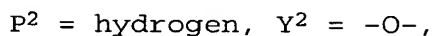
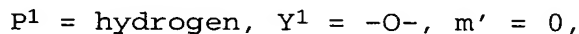
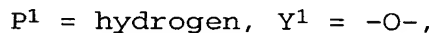
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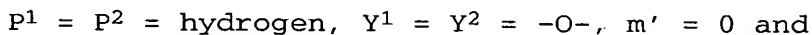
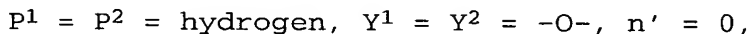
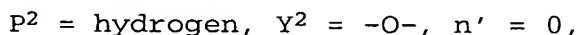
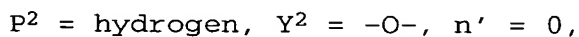
15 According to the definition of the X and Y radicals in the formulae IIa and IIb, the variables in the compounds listed are, in the same order in which they were listed, as follows:



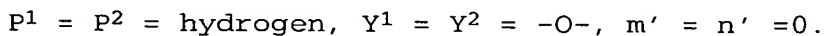
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Further, the hydroxyl group may be replaced by, for example, a carboxyl group ( $P^1 = \text{hydrogen}$  and  $Y^1 = -OCO-$  and/or  $P^2 = \text{hydrogen}$  and  $Y^2 = -COO-$ ). In the difunctional compounds, both hydroxyl and carboxyl groups may also be present.

45

## 10

These hydroxyl or carboxylic acid or hydroxyl/carboxylic acid compounds which are given by way of example are again to be regarded as direct products of the preparative process according to the invention.

5

The reactants of the formulae Ia and Ib are customarily dissolved in a molar ratio of from 2:1 to 1:2 together with the at least one metal compound and the at least one base in the inert solvent. The solution is normally prepared at room temperature, but in individual cases, may also be prepared at higher or lower temperatures.

The temperature during the actual reaction under the action of microwave radiation is not critical. Customarily, the reaction is carried out at temperatures from room temperature to the boiling temperature of the solvent used.

Preference is given to using dimethylformamide ("DMF"), N-methylpyrrolidone ("NMP") or a mixture of the two as solvent. Particular preference is given to using DMF as solvent (or as suspending medium) in the process according to the invention.

Preference is given to selecting the at least one base from the group consisting of alkali metal carbonates, alkali metal phosphates and tri(C<sub>1</sub>-C<sub>4</sub>-alkyl)amines, and emphasis is given to the alkali metal carbonates.

The group of suitable bases includes in particular sodium carbonate, potassium carbonate, sodium phosphate and potassium phosphate, trimethyl-, triethyl- and triisopropylamine.

Particular preference is given to using potassium carbonate.

In individual cases, the addition of potassium iodide may also be advantageous for the reaction. Whether there is such a positive effect and how much potassium iodide should optionally be added can be easily determined by preliminary experiments.

The output of the microwave radiation source is customarily from ten to hundreds of watts and should be selected according to the volume of the reaction batch. The correct power of the radiation source is customarily known to those skilled in the art and/or can be easily determined by preliminary experiments.

The alkyne compounds obtained are worked up and purified by customary organic synthesis methods.

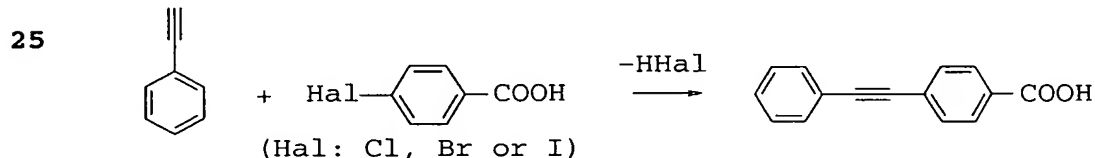
Examples:

The experiments described hereinbelow use the following:

5	Substance	Source	Purity
	4-Chlorobenzoic acid	Acros	>99%
	4-Bromobenzoic acid	Merck	>99%
	4-Iodobenzoic acid	EMKA-Chemie	>99%
10	Phenylacetylene	Aldrich	>98%
	Copper(I) iodide	Merck	>99%
	Triphenylphosphine	Merck	>99%
	Potassium carbonate (ground)	Merck	>99.9%
15	Dimethylformamide ("DMF")	BASF	>99%
	Potassium iodide	J.T.Baker	>99%

## 20 Experimental procedure:

General reaction equation:



- 30 5 mmol of 4-halobenzoic acid (halo: chloro, bromo or iodo), 7.5 mmol of phenylacetylene, 0.5 mmol of copper(I) iodide, 1.0 mmol of triphenylphosphine, 7.5 mmol of potassium carbonate and 10 ml of DMF were initially charged under an argon atmosphere into a 100 ml four-neck flask provided with a magnetic stirrer,
- 35 heated within 5 min to a temperature of 155°C and subjected at reflux for 20 min to the maximum radiation output of a microwave device (MLS-Ethos 1600; unpulsed; magnetron frequency 2450 MHz; maximum output 375 W).
- 40 The workup was carried out by filtering off the solid (substantially in potassium carbonate), washing with 100 ml of dichloromethane and extracting the solution obtained three times with 50 ml each time of a saturated, aqueous sodium chloride solution. The dichloromethane solution was dried over sodium
- 45 sulfate and then the solvent was removed on a rotary evaporator.

## 12

For comparative purposes, experiments were also carried out with the addition of 0.5 mmol of potassium iodide. The amounts of the remaining substances used were unchanged; the experimental procedure and workup were likewise identical to those described 5 above.

## Results:

The experimental results are reported in the following table.

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Example	Yield (% of theory)	Potassium iodide addition	4-Halobenzoic acid Halo =
1 (Comparative)	33.0	-	I
15 2	74.4	-	Cl
3	56.5	+	Cl
4	54.5	-	Br
5	38.6	+	Br

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When 4-iodobenzoic acid was used (example 1 (comparative), the lowest yields by far were obtained, but when 4-bromo- and in particular 4-chlorobenzoic acid were used (examples 4 and 5, and 2 and 3 respectively), distinctly higher yields of the desired target compound were obtained. In the experiments carried out 25 here, the addition of potassium iodide (examples 3 and 5) caused a deterioration compared to the potassium iodide-free experimental procedure (examples 2 and 4). However, it is conceivable that, in individual cases, the addition of potassium 30 iodide may have an advantageous effect.

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